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ORIGINAL REPORT

Cost Effectiveness and Screening Interval of Lipid Screening in Hodgkin's Lymphoma Survivors

Aileen B. Chen, Rinaa S. Punglia, Karen M. Kuntz, Peter M. Mauch, and Andrea K. Ng

From the Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA; and Division of Health Policy and Management, School of Public Health, University of Minnesota, Minneapolis, MN.

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Corresponding author: Aileen Chen, MD, MPP, Dana-Farber Cancer Institute, 44 Binney St – Smith 255, Boston, MA 02115; e-mail: achen7@partners.org.

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ABSTRACT

Purpose
Survivors of Hodgkin's lymphoma (HL) who received mediastinal irradiation have an increased risk of coronary heart disease. We evaluated the cost effectiveness of lipid screening in survivors of HL and compared different screening intervals.

Methods
We developed a decision-analytic model to evaluate lipid screening in a hypothetical cohort of 30-year-old survivors of HL who survived 5 years after mediastinal irradiation. We compared the following strategies: no screening, and screening at 1-, 3-, 5-, or 7-year intervals. Screen-positive patients were treated with statins. Markov models were used to calculate life expectancy, quality-adjusted life expectancy, and lifetime costs. Baseline probabilities, transition probabilities, and utilities were derived from published studies and US population data. Costs were estimated from Medicare fee schedules and the medical literature. Sensitivity analyses were performed.

Results
Using an incremental cost-effectiveness ratio (ICER) threshold of $100,000 per quality-adjusted life-year (QALY) saved, lipid screening at every interval was cost effective relative to a strategy of no screening. When comparing screening intervals, a 3-year interval was cost effective relative to a 5-year interval, but annual screening, relative to screening every 3 years, had an ICER of more than $100,000/QALY saved. Factors with the most influence on the results included risk of cardiac events/death after HL, efficacy of statins in reducing cardiac events/death, and costs of statins.

Conclusion
Lipid screening in survivors of HL, with statin therapy for screen-positive patients, improves survival and is cost effective. A screening interval of 3 years seems reasonable in the long-term follow-up of survivors of HL.

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INTRODUCTION

Modern treatment techniques have improved the long-term survival of patients with Hodgkin's lymphoma (HL). More than 75% of patients achieve long-term freedom from relapse, and early-stage patients have cure rates exceeding 90%.[1-4] Although the risk of death from HL decreases over time, survivors continue to be at increased risk of mortality from late effects of treatment and other causes.[4-9] Consequently, survivorship issues have become increasingly important, and there is a growing need for more data on the appropriate screening strategies for late effects in these patients.[7]

Cardiovascular disease is the second leading cause of death in survivors of HL who received mediastinal irradiation, after second malignancies, and survivors have an increased risk of cardiac morbidity and death compared with the general population.[4,8-15] Prior studies of patients with HL suggest that traditional cardiac risk factors further contribute to treatment-related cardiovascular disease.[13,16,17] Therefore, a rational strategy to reduce risk of cardiac disease in long-term HL survivors is to screen for treatable risk factors, one example being hyperlipidemia. Large randomized studies in the cardiac literature, including the West of Scotland Coronary Prevention Study and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial, have demonstrated a survival benefit in patients with hyperlipidemia who are treated with statins for primary prevention of coronary heart disease (CHD).[18,19] Guidelines are available on lipid screening in HL survivors, although recommendations on the frequency of screening are variable. The American

College of Radiology recommends periodic lipid screening of survivors of HL,[20] the National Comprehensive Cancer Network recommends annual lipid screening,[21] and the Childhood Oncology Group recently changed its recommendation from lipid screening every 3 to 5 years to every 2 years.[22] Moreover, these guidelines were established based on consensus of expert opinion, rather than existing evidence. The effectiveness and cost effectiveness of screening in these patients, as well as the optimal screening interval, are currently unknown. We have developed a decision-analytic model to assess the effectiveness and cost effectiveness of lipid screening and to determine an appropriate screening interval for survivors of HL who have received mediastinal irradiation.

METHODS

Model Structure

We constructed a Markov decision-analytic model to evaluate lipid screening strategies in survivors of HL who received mediastinal irradiation. We evaluated a hypothetical cohort of 30-year-old patients who survived 5 years after HL treatment. A Markov state-transition model was used to estimate life expectancy and quality-adjusted life expectancy (QALE).[23] QALE was calculated by multiplying time spent by patients in each health state by the corresponding health-related quality-of-life weights or utilities.[24]

Survivors of HL could transition between various health states including no hyperlipidemia, undetected/untreated hyperlipidemia, treated hyperlipidemia, postcardiac event, and death. Annual transition probabilities were dependent on age, sex, time interval since initial treatment, and lipid status. In each cycle, patients were at risk of dying from HL, second malignancies, cardiac disease, or other causes. The model was run in 1-year cycles until the entire cohort had died. Expected costs were incurred as patients transitioned between health states and events during their life span. Separate analyses were performed for women and men as a result of differing risks for cardiac disease, hypercholesterolemia, and death. Figure 1 shows a state diagram representing our model's structure.

We evaluated the following lipid screening strategies: no screening, annual screening, screening every 3 years, screening every 5 years, and screening every 7 years. If a survivor was found to have hyperlipidemia, then treatment with statins was initiated. Screening was discontinued after age 65 years as a result of low rates of developing new hyperlipidemia in this age group. However, older patients already on statins for hyperlipidemia continued on statins.[25] The incremental cost-effectiveness ratio (ICER) for each strategy was calculated by dividing the incremental cost by the incremental effectiveness, measured in life-years and quality-adjusted life-years (QALY). In our model, each incremental cost-effectiveness value represents a comparison with the next least frequent screening interval. ICER and costs were rounded to the nearest $100.

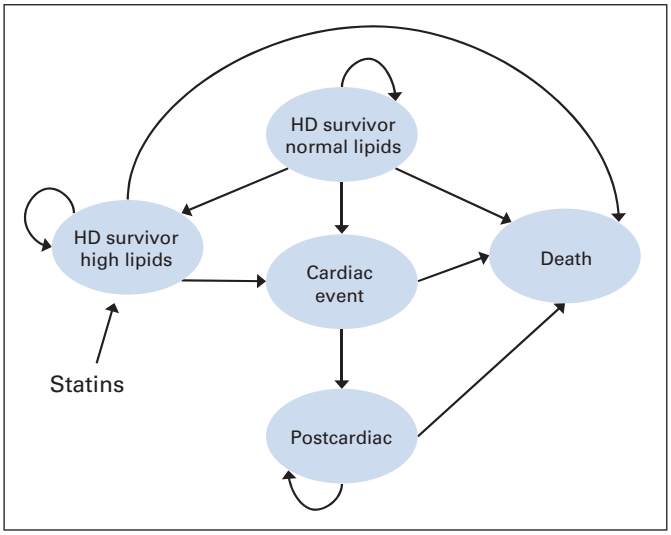

Fig 1. State diagram – model structure. Survivor of Hodgkin's disease (HD) high lipid state can be undetected or detected and treated with statins. Postcardiac state consists of multiple states depending on age at time of event.

Analyses were performed from a modified societal perspective and included medical costs from screening and treatment, as well as downstream costs. Costs and benefits were discounted at an annual rate of 3%, as recommended by the Panel on Cost-Effectiveness in Health and Medicine.[26] TreeAge Pro Suite 2008 (TreeAge Software, Williamstown, MA) was used to design the model and perform analyses.

Key Assumptions

We assumed that survivors of HL did not have pre-existing clinical CHD and that the incidence of hyperlipidemia in survivors of HL was similar to that for the age- and sex-matched US population. This is consistent with survey results from survivors of HL and siblings from our institution.[27] In the baseline analysis, we assumed that survivors of HL who screened positive for hyperlipidemia had the same compliance rates and relative risk reduction in CHD from statins as observed in randomized trials of patients without HL.[18,19] Furthermore, we assumed that, after a coronary event, survivors of HL had the same risk of coronary death as patients without HL and that costs of follow-up and treatment after a cardiac event would be similar. This is consistent with the observation that the magnitudes of the increased risk of CHD and the increased risk of cardiac death in survivors of HL seem to be similar in published data.[4,28]

Baseline Estimates

Baseline estimates for the age- and sex-matched probability of dying from cardiac and noncardiac disease were estimated from the 2000 US Life Tables[29] and adjusted to reflect the increased relative risk of cardiac death in survivors of HL. We used a baseline relative risk for cardiac mortality of 3.2, as reported by Ng et al.[4] Although estimates have varied, this is within the range of most other studies.[8-11,14] We also accounted for the increased risk of death from HL and second malignancy.[4]

The annual incidence of developing hyperlipidemia was derived by calibrating our model to approximate observed age- and sex-matched prevalence data calculated from the 1999 to 2002 National Health and Nutrition Examination Survey, based on either a measured total cholesterol greater than 240 mg/dL or the current use of medication for hyperlipidemia.[30] The age- and sex-adjusted annual probability of having a cardiac event was estimated using data from the Framingham Heart Study and was adjusted to account for relative risk of having a cardiac event with elevated versus unelevated cholesterol levels.[31] We used the Framingham definition of a hard CHD event, which included myocardial infarction, coronary insufficiency, and CHD death. We then accounted for the increased risk of CHD in survivors of HL. Age-adjusted risk of death over time after a cardiac event was derived from the Worcester postcardiac long-term survival data.[32]

Utility values after a cardiac event were derived from time trade-off scores from the Beaver Dam Outcomes Study. There was no observed utility decrement from hyperlipidemia alone.[33] We also did not assume a utility decrement from statin therapy for hyperlipidemia in our baseline analysis. However, to account for potential adverse effects from the treatment, disutility associated with statin use was tested in the sensitivity analysis. A utility value of 1.00 was used to represent a survivor of HL in good health without cardiac disease.

Costs

Costs were derived from the 2006 Medicare fee schedules,[34] the Red Book pharmacy reference,[35] and the medical literature and were converted to 2006 US dollars based on the medical care component of the Consumer Price Index.[36] Costs of screening included a lipid panel, which we assumed could be incorporated into a routine HL follow-up or primary care visit. Patients who were screen positive received statin therapy. We used the average

wholesale price for atorvastatin, the most commonly prescribed statin, in our baseline estimate, but costs of alternative statins, including pravastatin and simvastatin, now available in generic formulation, were considered in the sensitivity analysis.[35] In the first year, patients on statins received two liver function tests, as recommended in the atorvastatin package insert,[37] and an additional office visit. In subsequent years, they received one liver function test and one lipid panel, which were incorporated into a regular follow-up visit. They were treated from the time of diagnosis until death.

We used published costs of nonfatal and fatal cardiac events in the first year, as well as subsequent annual costs, as estimated by Russell et al.[38] Estimates from multiple other studies fell within the range specified by our sensitivity analysis.[39-42]

Sensitivity Analyses

Sensitivity analyses were performed to evaluate the stability of our model to uncertainties in the estimates of key variables. We varied the estimates for costs and probabilities within ranges reported in the literature, or from 50% to 200% of the baseline values. We varied patient utility with hyperlipidemia from 0.99 to 1.00. The annual discount rate was varied from 0% to 5%. Table 1 lists the baseline estimates used in our model.

RESULTS

Baseline Analysis

Our analysis showed that men and women who survived at least 5 years after HL lived, on average, to ages 64.4 and 75.7 years, respectively. Furthermore, HL survivors screened for hyperlipidemia had a longer life expectancy than unscreened survivors. For example, the life expectancy for a patient screened every 3 years was 3.8 months longer for men and 8.7 months longer for women compared with a strategy of no screening. QALE was also greater for screened versus unscreened survivors. The lifetime costs, life

Table 1. Baseline Estimates

Variable	Baseline Estimate	Reference
Risk of cardiac events and mortality in survivors of HL		
RR of cardiac event or cardiac death after HL	3.20	Ng et al[4]
Probability of death after MI if age < 55 years–initial, %*	3.5	Goldberg et al[32]
Probability of death after MI if age < 55 years and survived initial event–year 1, %*	4.0	Goldberg et al[32]
Risk of second malignancy and HL death, %*		
Annual probability of death from HL–year 5 after HL	0.5	Ng et al[4]
Annual probability of death from second malignancy–year 5 after HL	0.4	Ng et al[4]
Risk of developing hyperlipidemia, %*		
Prevalence at age 30 years–men	10.0	National Center for Health Statistics[30]†
Annual probability of developing hyperlipidemia at age 30 years–men	1.4	National Center for Health Statistics[30]†
Prevalence at age 30 years–women	9.0	National Center for Health Statistics[30]†
Annual probability of developing hyperlipidemia at age 30 years–women	0.6	National Center for Health Statistics[30]†
Risk of cardiac events and death with treated and untreated hyperlipidemia		
RR of cardiac event without hyperlipidemia (normal or borderline)	1	Wilson et al[31]‡
RR of cardiac event with hyperlipidemia–men	1.64	Wilson et al[31]‡
RR of cardiac event with hyperlipidemia–women	1.38	Wilson et al[31]‡
RR of cardiac events and death with treated *v* untreated hyperlipidemia	0.69	Downs et al[18]; Shepherd et al[19]
Costs, adjusted to 2006 $		
Lipid panel	26	US Department of Health and Human Services[34]
Statin–annual	944	2007 Red Book[35]
Atorvastatin	944	
Pravastatin (generic)	336	
Liver function test	11	US Department of Health and Human Services[34]
Level 2 office visit	93	US Department of Health and Human Services[34]
Nonfatal MI–year 1	23,694	Russell et al[38]
Fatal MI–year 1	26,731	Russell et al[38]
Post-MI–annual cost after year 1	1,602	Russell et al[38]
Quality of life weights (utilities)		
Good health	1.00	
Hyperlipidemia on statins	1.00	Fryback et al[33]‡
Post-MI	0.84	Fryback et al[33]‡
Discount rate–annual, %	3	Weinstein et al[26]

Abbreviations: HL, Hodgkin's lymphoma; RR, relative risk; MI, myocardial infarction.
*Estimated as a function of age and/or time after event. The table shows the baseline estimate for the first cycle (year).
†Calculated directly from data.
‡Adapted from study data.

expectancy, and QALE for no screening, as well as each screening interval, are listed in Table 2.

Using a threshold of $100,000 per QALY saved, we found that lipid screening, at any of the tested intervals, was cost effective compared with a strategy of no screening, ranging from $22,700 per QALY saved for 7-year screening to $26,700 for annual screening compared with no screening. To compare different screening intervals to each other, the cost per QALY saved for each screening interval was compared with the next least frequent interval to calculate an ICER. Accounting for costs incurred by screening, treatment, monitoring for treatment-related complications, and cardiac disease, as well as discounting over time, we found that the ICER increased with successively shorter screening intervals. For example, screening annually cost $125,500 per QALY saved compared with a 3-year screening interval in men. However, screening every 5 years cost only an additional $31,700 per QALY saved compared with a 7-year interval. Using a threshold of $100,000 per QALY saved, lipid screening every 3 years seems cost effective compared with screening every 5 years, but screening annually would no longer be cost effective compared with screening every 3 years. These results apply to both men and women, although the ICER was generally higher in women than in men. Full results are listed in Table 2.

Sensitivity Analysis

Lipid screening at any of the tested intervals, compared with a strategy of no screening, was cost effective at a threshold of $100,000 per QALY saved within the range of all variables tested on sensitivity analysis. As an example, Figure 2 shows the relative sensitivity of our model to key variables for screening every 3 years compared with no screening in male survivors of HL. However, appropriate screening interval was sensitive to several variables in our model, listed in Table 3, for men. Results for women were similar, although lipid screening was somewhat less cost effective overall (data not shown).

Appropriate screening interval was sensitive to the effectiveness, disutility, and costs associated with statin therapy. With decreasing effectiveness of statins, longer screening intervals were appropriate, whereas shorter screening intervals became more appropriate with increasing effectiveness. Differences in compliance rates in survivors of HL, compared with statin trial participants, might also alter the observed effectiveness of statins. Because statins are generally well tolerated, we did not assume a decrement in utility from treatment for our baseline analysis. However, our sensitivity analysis showed that it became less cost effective to screen at shorter intervals if patients experienced disutility from taking statins. Furthermore, the ICER of different screening intervals was sensitive to the cost of statin therapy. For example, when we used the cost of the most commonly prescribed statin, atorvastatin, and an ICER threshold of $100,000 per QALY saved in our baseline analysis, the most appropriate screening interval was every 3 years. However, when we used the cost of pravastatin or simvastatin, available in generic formulation, it became marginally cost effective to screen annually in men, with an ICER of $97,000, although for women, every 3 years was still more appropriate.

Appropriate screening interval was also sensitive to the relative risk of developing CHD after treatment for HL. Studies of survivors of HL have varied in their estimates of risk of cardiac death after mediastinal radiation, so we performed sensitivity analyses over a broad range, from a relative risk of cardiac death of 1.6 to 6.4 in survivors of HL compared with the general population. We found that the appropriate screening interval ranged from annually (for relative risk of 6.4) to every 5 years (for relative risk of 1.6) in both men and women.

The optimal screening interval was also sensitive to the discount rate used in the model. We used the recommended baseline discount

Table 2. Baseline Analysis for Lipid Screening Compared With No Screening

Outcome	No Screening	Screening (interval between tests)			
		7 Years	5 Years	3 Years	1 Year
Men					
Without discounting					
Life expectancy, months	412.35 (34.36)*	416.02	416.14	416.19	416.27
QALE, months	399.04 (33.25)	403.61	403.77	403.84	403.94
Costs, 2006 $†	26,300	31,600	31,900	32,100	32,700
With discounting‡					
QALE, months	235.15 (19.60)	236.74	236.81	236.84	236.89
Costs, 2006 $†	11,100	14,100	14,300	14,500	14,800
Incremental cost-effectiveness ratio, $/QALY†§		22,700	31,700	78,200	125,500
Women					
Without discounting					
Life expectancy, months	548.44 (45.70)	556.88	557.05	557.16	557.29
QALE, months	545.09 (45.42)	553.92	554.11	554.23	554.37
Costs, 2006 $†	19,400	30,700	31,100	31,500	32,300
With discounting‡					
QALE, months	292.03 (24.34)	294.20	294.26	294.30	294.34
Costs, 2006 $†	5500	10,400	10,600	10,900	11,600
Incremental cost-effectiveness ratio, $/QALY†§		27,000	42,800	97,900	165,400

Abbreviations: QALE, quality-adjusted life expectancy; QALY, quality-adjusted life-year.
*Years are shown in parentheses.
†Rounded to nearest $100.
‡Adjusted for 3% annual discount rate.
§Comparisons done relative to next most frequent screening interval.

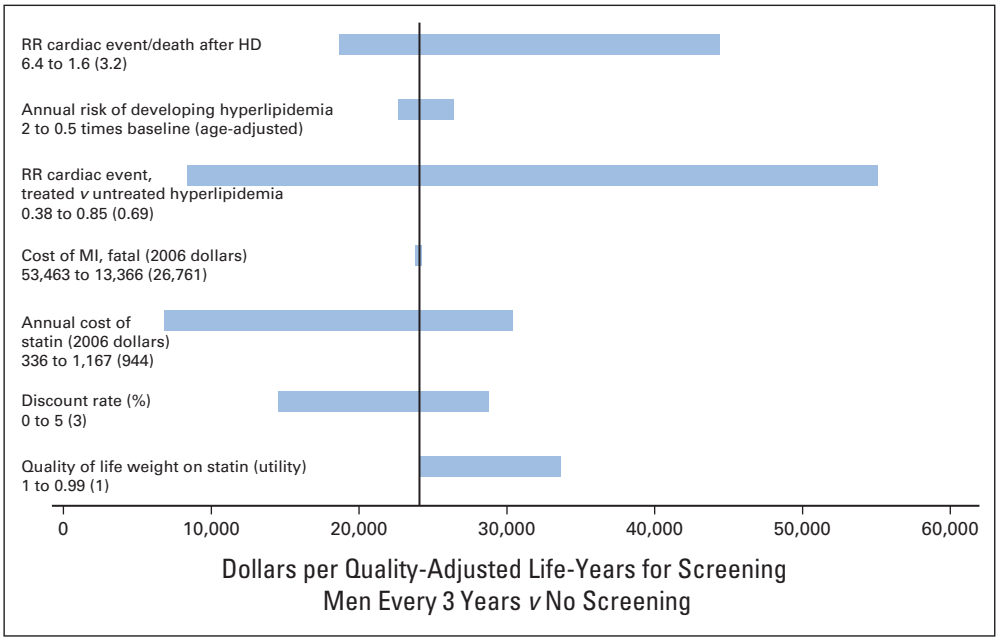

Fig 2. Sensitivity to key variables for screening every 3 years, compared with no screening, in men. NOTE. Sensitivity analysis done within the range listed. Baseline estimates in parentheses. RR, relative risk; HD, Hodgkin's disease; MI, myocardial infarction.

rate of 3% per year,[26] but if costs and benefits were not discounted over time, then shorter screening intervals became more cost effective.

Our model was relatively insensitive to costs associated with myocardial infarction, subsequent costs in the years after a cardiac event, and costs associated with screening tests and office visits. It was also relatively insensitive to annual risk of developing hyperlipidemia.

DISCUSSION

Multiple retrospective studies have confirmed that survivors of HL treated with mediastinal irradiation are at increased risk of cardiac morbidity and death,[3-7,9,10,13,16,17,28] and there has been a growing recognition that these patients may benefit from screening and risk reduction interventions.[4,7-11,14] One potential strategy is lipid screening, a low-cost, widely available intervention that can be performed by oncology specialists and primary care physicians. Statins have been shown in randomized trials to reduce cardiac events and mortality in patients with hyperlipidemia. Prior studies analyzing the cost effectiveness of statin therapy for primary prevention of cardiac disease in patients with hyperlipidemia have given varied results, depending on underlying risk factors,[43,44] and have not typically addressed the question of appropriate screening interval. With limited data on appropriate lipid screening strategies, expert groups in North America have given a range of screening recommendations for the general population.[45-49] For survivors of HL, the available recommendations are also variable and are consensus based rather than evidence based.[20-22]

In our decision-analytic model, using available data from the literature, we found that lipid screening in survivors of HL, beginning 5 years after treatment, improved survival. Furthermore, lipid screening was a cost-effective intervention compared with no screening. This finding was robust within a wide range of sensitivity analyses. Other studies of cost effectiveness of medical interventions in the United States have frequently used a threshold of $100,000 per QALY saved, although the appropriate threshold to be used depends on societal judgments and available resources, and our results should be interpreted in this light.

With respect to screening interval, we found that an interval of every 3 years was most appropriate when using our baseline estimates and a threshold of $100,000 per QALY saved. However, on sensitivity analysis, we found that the appropriate screening interval was sensitive to several variables in our model, including cost of statins, relative risk of cardiac disease in survivors of HL, and effectiveness of statins. Although we used the cost of the most commonly prescribed statin in our model, patients are increasingly being switched to generic alternatives. If we used the cost of generic statins in our model, then a screening interval of every year became appropriate in men, but a screening interval of every 3 years was still supported for women.

Limitations of our model include the assumptions regarding risk of cardiac events, hyperlipidemia, and survival in survivors of HL. We assumed that survivors of HL develop hyperlipidemia at a similar rate as the general population, respond similarly to statins, and have a similar risk of death after cardiac events. However, there are no clear reasons or data to suggest otherwise. We used a conservative total cholesterol threshold to screen for hyperlipidemia. However, low-density lipoprotein, high-density lipoprotein, and concomitant risk factors are also important in determining the appropriate treatment threshold and target cholesterol for individuals.[49] A lower threshold would find more patients with hyperlipidemia, although the ICER of treating these patients would likely be lower. Our model also does not address heterogeneity in other underlying cardiac risk factors among survivors, and these risk factors may further contribute to risk of cardiac complications after HL therapy.[13,16,28] Finally, HL treatment has evolved over time, and our results may not apply to patients currently receiving therapy. Estimates of long-term risk of cardiac disease after HL treatment are based mainly on patients treated from the 1970s to 1990s who received radiation to larger fields and higher

Table 3. Sensitivity Analyses on Key Estimates for Different Screening Intervals in Men

Variable	Baseline Estimate	Variable Range Tested	ICER ($/QALY)			
			1 *v* 3 Years	3 *v* 5 Years	5 *v* 7 Years	7 Years *v* No Screening
Risk of cardiac events and mortality in survivors of HL						
RR of cardiac event or cardiac death after HL	3.20	1.60	293,500	180,400	73,200	41,700
		6.40	80,800	51,200	20,900	17,600
Risk of developing hyperlipidemia*						
Annual probability of developing hyperlipidemia at age 30 years	1.4%	0.70%	210,700	101,700	36,200	24,900
		2.80%	84,700	68,700	30,600	21,200
Risk of cardiac events and death with treated and untreated hyperlipidemia						
RR of cardiac event with hyperlipidemia	1.64	1.32	120,500	84,800	36,400	25,500
		2.28	78,900	55,900	23,600	19,300
RR of cardiac events and death with treated *v* untreated hyperlipidemia	0.69	0.38	53,900	32,400	12,200	7,700
		0.85	266,700	168,300	70,000	52,100
Costs, adjusted to 2006 dollars						
Statin–annual	944	336	97,000	41,000	12,100	5,900
		1,167	135,900	91,800	39,000	28,800
Nonfatal MI–year 1	23,694	11,847	126,800	79,600	33,000	24,000
		47,388	122,900	75,300	29,300	20,100
Fatal MI–year 1	26,731	13,366	125,500	78,200	31,900	22,800
		53,463	125,300	78,100	31,500	22,400
Post-MI–annual cost after year 1	1,602	801	126,900	79,800	33,100	23,900
		3,205	122,600	75,000	29,100	20,300
Quality of life weights (utilities)						
Hyperlipidemia on statins	1	0.99	235,900	200,900	47,000	31,300
Post-MI	0.85	0.70	99,600	60,700	25,700	18,700
		0.93	148,000	94,000	36,900	26,100
Discount rate–annual	3%	0%	61,900	43,600	19,000	13,900
		5%	192,500	112,100	43,800	31,800

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; HL, Hodgkin's lymphoma; RR, relative risk; MI, myocardial infarction.
*Estimated as a function of age. The table shows the baseline estimate and range tested for the first cycle (year).

doses than are currently used. Typical radiation doses were approximately 36 Gy to the mediastinum, and most patients received extended-field radiation, which often included mantle and para-aortic or total nodal irradiation fields. If chemotherapy was administered, involved-field radiation was more commonly used. Patients treated in the modern era may have lower risk of cardiac disease, making lipid screening less cost effective. However, increasing data are available on the cardiotoxicity of doxorubicin-based chemotherapy in patients with HL,[10,50,51] and the cardiac risks associated with doxorubicin in combination with less extensive radiation still need to be elucidated. The sensitivity analysis considers the potential impact of changes in cardiac risk that could occur from changes in treatment practice, but this was not explicitly modeled because of limited long-term risk data for these patients. Therefore, our model applies primarily to the majority of survivors of HL who have already received treatment with larger radiation fields for whom providers must make recommendations and in whom screening guidelines are currently needed.

As cancer treatment continues to improve, greater attention will need to be devoted to the late effects of treatment and long-term follow-up of survivors. Our study suggests that lipid screening is likely to reduce cardiac deaths and to be cost effective compared with other medical interventions. Furthermore, our results indicate that a screening interval of every 3 years is reasonable for the average patient with HL. However, appropriate screening interval for individual patients should also consider other costs, cardiovascular risk factors, and treatment history, with more frequent screening considered for survivors felt to be at higher risk.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Aileen B. Chen, Rinaa S. Punglia, Karen M. Kuntz, Andrea K. Ng
Collection and assembly of data: Aileen B. Chen
Data analysis and interpretation: Aileen B. Chen, Rinaa S. Punglia, Karen M. Kuntz, Peter M. Mauch, Andrea K. Ng
Manuscript writing: Aileen B. Chen, Rinaa S. Punglia, Karen M. Kuntz, Andrea K. Ng
Final approval of manuscript: Aileen B. Chen, Rinaa S. Punglia, Karen M. Kuntz, Peter M. Mauch, Andrea K. Ng

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